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TITLE: Compositions and methods for eliciting CTL immunity

PUBLICATION-DATE: May 29, 2003

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/130.1; 424/133.1, 424/143.1, 424/147.1, 435/345, 530/300

CLAIMS:

What is claimed is:

1. An immunogenically effective composition comprising: a first peptide comprising an epitope, wherein the first peptide binds to an HLA class I molecule to form an epitope-HLA complex recognized by a human cytotoxic T cell; a second peptide comprising an epitope, wherein the second peptide binds to an HLA class II molecule to form an epitope-HLA complex recognized by a human helper T cell; an adjuvant; and a physiologically acceptable carrier.

2. The composition of claim 1, wherein the second peptide is covalently linked to the first peptide.

3. The composition of claim 1, wherein the second peptide is not linked to the first peptide.

4. The composition of claim 1, wherein the first peptide is linked to the second peptide by a spacer molecule.

5. The composition of claim 1, wherein the epitope is a viral epitope, a bacterial epitope, a parasitic epitope, or a tumor epitope.

6. The composition of claim 1, wherein the first peptide, the second peptide, or the first peptide and second peptide are each from six to thirty amino acid residues in length.

7. The composition of claim 1, wherein the first peptide, the second peptide, or the first peptide and second peptide comprises a plurality of epitopic units.

8. The composition of claim 1, wherein the first peptide is elected from the group consisting of LLAQFTSAI (SEQ ID NO:31), LLVPFVQWFV (SEQ ID NO:32), WLSLLVPFV (SEQ ID NO:33), FLLAQFTSA (SEQ ID NO:34), FLLSLGIHL (SEQ ID NO: 35), ALMPLYACI (SEQ ID NO:36), ILLLCLIFLL (SEQ ID NO:37), KLHLYSHPI (SEQ ID NO:38), VLLDYQGML (SEQ ID NO:39), LLPIFFCLWV (SEQ ID NO:40), VLQAGFFLL (SEQ ID NO:41), YLHTLWKAGI (SEQ ID NO:42),

YLHTLWKAGV (SEQ ID NO:43), PLLPIFFCL (SEQ ID NO:44), ILSTLPETTV (SEQ ID NO:45), LLFNILGGWV (SEQ ID NO: 46), LLALLSCLTV (SEQ ID NO:47), YLVAYQATV (SEQ ID NO:48), FLLLADARV (SEQ ID NO:49), ILAGYGAGV (SEQ ID NO:50), DLMGYIPLV (SEQ ID NO:51), YLLPRRGPRL (SEQ ID NO:52), ALSTGLIHL (SEQ ID NO:53), LLALLSCLTI (SEQ ID NO:54), RLIVFPDLGV (SEQ ID NO:55), RLHGLSAFSL (SEQ ID NO:56), ILGGWVAAQL (SEQ ID NO:57), SMVGNWAKV (SEQ ID NO:58), YLVTRHADV (SEQ ID NO:59), VLAALAAYCL (SEQ ID NO:60), LLMGTLGIV (SEQ ID NO:65), YMLDLQPET (SEQ ID NO:66), FAFRDLCIV (SEQ ID NO:67), TLGIVCPIC (SEQ ID NO:68), TLHEYMLDL (SEQ ID NO:69), GTLGIVCPI (SEQ ID NO:70), MLDLQPETT (SEQ ID NO:71), TIHDIILECV (SEQ ID NO:72), VLAEAMSQV (SEQ ID NO:73), LLWKGEGAVV (SEQ ID NO:74), LLWKGEGAV (SEQ ID NO:75), ILKEPVHGV (SEQ ID NO:76), IVGAETFYV (SEQ ID NO:77), IIGAETFYV (SEQ ID NO:78), LWVTVYYGV (SEQ ID NO:79), LMVTVYYGV (SEQ ID NO:80), KMVELVHFL (SEQ ID NO:81), KMVELVHFLL (SEQ ID NO:82), LVFGIELMEV (SEQ ID NO:83), KVLEYVIKV (SEQ ID NO:84), KVADLVGFLL (SEQ ID NO:85), KVAEFVHFL (SEQ ID NO:86), CILESLFRA (SEQ ID NO:87), FLWGPRALA (SEQ ID NO:88), VMIAMEGGHA (SEQ ID NO:89), LVLGTLEEV (SEQ ID NO:90), ALREEEEGV (SEQ ID NO:91), ALAETSYVKV (SEQ ID NO:92), YVIKVSARV (SEQ ID NO:93), and RALAETSYV (SEQ ID NO:94).

9. The composition of claim 1, wherein the second peptide is selected from the group consisting of QYIKANSKFIGITE (SEQ ID NO:95), KIAKMEKASSVFNVVNS (SEQ ID NO:96), DIEKKIAKMEKASSVFNVVNS (SEQ ID NO:97), ISQAVHAAHAEINE (SEQ ID NO:98), PKYVKQNTLKLAT (SEQ ID NO:99), MDIDPYKEFGATVELLSFLP (SEQ ID NO:100), PHHYALRQAILCWGELMYLA (SEQ ID NO:101), LLWFHISCLTFGRETVIEYL (SEQ ID NO:102), EYLVSFGVWIRTPPA (SEQ ID NO:103), and VSFGVWIRTPPAYRPPNAPI (SEQ ID NO:104).

10. The composition of claim 1, wherein the adjuvant is incomplete Freund's adjuvant, complete Freund's adjuvant, alum, aluminum hydroxide, or a lipid.

11. The composition of claim 1, wherein the adjuvant is a lipid.

12. The composition of claim 11, wherein the lipid is linked to the first peptide.

13. The composition of claim 11, wherein the lipid is linked to the second peptide.

14. The composition of claim 11, wherein the lipid is linked to the first and the second peptide.

15. A method for stimulating an immune response in a human against an epitope, comprising the steps of: (a) providing a first peptide comprising an epitope, wherein the first peptide binds to an HLA class I molecule to form an epitope-HLA complex recognized by a human cytotoxic T cell; (b) providing a second peptide comprising an epitope, wherein the second peptide binds to an HLA class II molecule to form an epitope-HLA complex recognized by a human helper T cell; (c) providing an adjuvant; and (d) administering the first and second peptides and the adjuvant to the human.

16. The method of claim 15, wherein the second peptide is covalently linked to the first peptide.

17. The method of claim 15, wherein the second peptide is not linked to the first peptide.

18. The method of claim 15, wherein the first peptide is linked to the second peptide by a spacer molecule.

19. The method of claim 15, wherein the administration step comprises administering the first peptide, second peptide and the adjuvant concurrently.

20. The method of claim 15, which further comprises, following step (d), a step (e) administering the first and second peptides to the human, whereby the administration steps (d) and (e) are spaced a sufficient interval apart to optimize development of said immune response to the epitopes.

21. The method of claim 20, wherein the administration step (e) comprises administering the second peptide and the first peptide approximately four weeks after the administration step (d).

22. The method of claim 15, wherein the epitope is a viral epitope, a bacterial epitope, a parasitic epitope, or a tumor epitope.

23. The method of claim 15, wherein the first and second peptides are administered

prophylactically.

24. The method of claim 15, wherein the first peptide and/or the second peptide are each from six to thirty amino acid residues in length.

25. The method of claim 15, wherein the first peptide, the second peptide, or the first peptide and second peptide comprises a plurality of epitopic units.

26. The composition of claim 15, wherein the first peptide is selected from the group consisting of LLAQFTSAI (SEQ ID NO:31), LLVPFVQWFV (SEQ ID NO:32), WLSLLVPFV (SEQ ID NO:33), FLLAQFTSA (SEQ ID NO:34), FLLSLGIHL (SEQ ID NO: 35), ALMPLYACI (SEQ ID NO:36), ILLLCLIFLL (SEQ ID NO:37), KLHLYSHPI (SEQ ID NO:38), VLLDYQGML (SEQ ID NO:39), LLPIFFCLWV (SEQ ID NO:40), VLQAGFFLL (SEQ ID NO:41), YLHTLWKAGI (SEQ ID NO:42), YLHTLWKAGV (SEQ ID NO:43), PLLPIFFCL (SEQ ID NO:44), ILSTLPETTV (SEQ ID NO:45), LLFNILGGWV (SEQ ID NO: 46), LLALLSCLTV (SEQ ID NO:47), YLVAYQATV (SEQ ID NO:48), FLLLADARV (SEQ ID NO:49), ILAGYGAGV (SEQ ID NO:50), DLMGYIPLV (SEQ ID NO:51), YLLPRRGPRL (SEQ ID NO:52), ALSTGLIHL (SEQ ID NO:53), LLALLSCLTI (SEQ ID NO:54), RLIVFPDLGV (SEQ ID NO:55), RLHGLSAFSL (SEQ ID NO:56), ILGGWVAAQL (SEQ ID NO:57), SMVGNWAKV (SEQ ID NO:58), YLVTRHADV (SEQ ID NO:59), VLAALAAYCL (SEQ ID NO:60), LLMGTLGIV (SEQ ID NO:65), YMLDLQPET (SEQ ID NO:66), FAFRDLCIV (SEQ ID NO:67), TLGIVCPIC (SEQ ID NO:68), TLHEYMLDL (SEQ ID NO:69), GTLGIVCPI (SEQ ID NO:70), MLDLQPETT (SEQ ID NO:71), TIHDIILECV (SEQ ID NO:72), VLAEAMSQV (SEQ ID NO:73), LLWKGEGAVV (SEQ ID NO:74), LLWKGEGAV (SEQ ID NO:75), ILKEPVHGV (SEQ ID NO:76), IVGAETFYV (SEQ ID NO:77), IIGAETFYV (SEQ ID NO:78), LWVTVYYGV (SEQ ID NO:79), LMVTVYYGV (SEQ ID NO:80), KMVELVHFL (SEQ ID NO:81), KMVELVHFLL (SEQ ID NO:82), LVFGIELMEV (SEQ ID NO:83), KVLEYVIKV (SEQ ID NO:84), KVADLVGFLL (SEQ ID NO:85), KVAEFVHFL (SEQ ID NO:86), CILESLFRA (SEQ ID NO:87), FLWGPRALA (SEQ ID NO:88), VMIAMEGGHA (SEQ ID NO:89), LVLGTLEEV (SEQ ID NO:90), ALREEEEGV (SEQ ID NO:91), ALAETSYVKV (SEQ ID NO:92), YVIKVSARV (SEQ ID NO:93), and RALAETSYV (SEQ ID NO:94).

27. The composition of claim 15, wherein the second peptide is selected from the group consisting of QYIKANSKFIGITE (SEQ ID NO:95), KIAKMEKASSVFNVVNS (SEQ ID NO:96), DIEKKIAKMEKASSVFNVVNS (SEQ ID NO:97), ISQAVHAAHAEINE (SEQ ID NO:98), PKYVKQNTLKLAT (SEQ ID NO:99), MDIDPYKEFGATVELLSFLP (SEQ ID NO:100), PHHYALRQAILCWGELMYLA (SEQ ID NO:101), LLWFHISCLTFGRETVIEYL (SEQ ID NO:102), EYLVSFGVWIRTPPA (SEQ ID NO:103), and VSFGVWIRTPPAYRPPNAPI (SEQ ID NO:104).

28. The method of claim 15, wherein the first and the second peptides are administered with a physiologically-acceptable carrier.

29. The method of claim 15, wherein the adjuvant is alum, aluminum hydroxide, or a lipid.

30. The method of claim 15, wherein the first peptide is administered with the lipid.

31. The method of claim 30, wherein the adjuvant is a lipid and the first peptide is linked to the lipid.

32. The method of claim 15, wherein the second peptide is administered with the adjuvant.

33. The method of claim 32, wherein the second peptide is linked to the adjuvant.

34. The method of claim 15, wherein the first peptide and the second peptide are administered with an adjuvant.

35. The method of claim 34, wherein the first peptide and the second peptide are both linked to the adjuvant.

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Celis, Esteban	San Diego	CA	US	
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APPL-NO: 10/ 128711 [PALM]
DATE FILED: April 22, 2002

RELATED-US-APPL-DATA:
Application 10/128711 is a continuation-of US application 08/197484, filed February 16, 1994, US Patent No. 6419931
Application 08/197484 is a continuation-in-part-of US application 07/935811, filed August 26, 1992, ABANDONED
Application 07/935811 is a continuation-in-part-of US application 07/874491, filed April 27, 1992, ABANDONED
Application 07/874491 is a continuation-in-part-of US application 07/827682, filed January 29, 1992, ABANDONED
Application 07/827682 is a continuation-in-part-of US application 07/749568, filed August 26, 1991, ABANDONED

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US95/02121	1995US-PCT/US95/02121	February 16, 1995

INT-CL: [07] A61 K 39/395, A61 K 39/40, A61 K 39/42, C07 K 2/00, C07 K 4/00, C07 K 5/00, C07 K 7/00, C07 K 14/00, C07 K 16/00, C07 K 17/00, A61 K 38/00, C12 N 5/06, C12 N 5/16

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US-CL-CURRENT: 424/130.1; 424/133.1, 424/143.1, 424/147.1, 435/345, 530/300

REPRESENTATIVE-FIGURES: 18

ABSTRACT:

Cytotoxic T lymphocyte responses are effectively induced to an antigen of interest, particularly viral, bacterial, parasitic and tumor antigens. Compositions, including pharmaceutical compositions, of CTL-inducing peptide and an adjuvant or a lipidated peptide which induces a helper T cell (HTL) response stimulate the antigen specific CTL response. Among the viral antigens to which the CTL responses are effectively induced

in humans are those of hepatitis B. The CTL response may be optimized by a regimen of two or more booster administrations. Cocktails of two or more CTL inducing peptides are employed to optimize epitope and/or MHC class I restricted coverage.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation of U.S. application Ser. No. 08/197,484, filed Feb. 16, 1994 which is a continuation-in-part of U.S. application Ser. No. 07/935,811, filed Aug. 26, 1992, which is a continuation-in-part of U.S. application Ser. No. 07/874,491, filed Apr. 27, 1992 and now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/827,682, filed Jan. 29, 1992 and now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/749,568, filed Aug. 26, 1991 and now abandoned, each of which is incorporated herein by reference.

1: Eur J Immunol. 1994 Dec;24(12):3175-9. Related Articles, Links

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Identification of a naturally processed HLA A0201-restricted viral peptide from cells expressing human papillomavirus type 16 E6 oncoprotein.

Bartholomew JS, Stacey SN, Coles B, Burt DJ, Arrand JR, Stern PL.

Department of Immunology, Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester, GB.

Human papillomavirus (HPV) DNA encoding the oncogenic proteins E6 and E7 is usually retained in cervical carcinomas, implicating these proteins as potential target antigens for immune recognition in this virally associated tumor. We have characterized endogenously processed peptides eluted from major histocompatibility complex class I molecules in cells infected with a recombinant vaccinia expressing the HPV-16 E6 oncoprotein. The reverse-phase chromatography profile of peptides eluted from isolated HLA-A0201 molecules in cells expressing the E6 oncoprotein differs from that of cells not expressing E6. Sequential Edman degradation of novel peaks found in the peptide profiles from cells expressing HPV-16 E6 led to the identification of a naturally processed HLA-A0201-restricted E6 peptide of sequence KLPQLCTEL. This approach has allowed the identification of a viral peptide which is processed and presented by cells expressing the E6 oncoprotein and is a likely target for cytotoxic T lymphocyte recognition in HLA-A0201-positive patients.

PMID: 7805746 [PubMed - indexed for MEDLINE]

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